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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,162	03/07/2002	Yoshihiro Sowa	14875-085001	4957

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EXAMINER	
GODDARD, LAURA B	
ART UNIT	**PAPER NUMBER**
1642	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,162	SOWA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-10,14-17,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-10,14-17,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed July 9, 2007 in response to the Office Action of April 9, 2007, is acknowledged and has been entered. Previously pending claim 6 has been amended. Claim 29 was canceled. Claims 6-10, 14-17, 27, and 28 are currently pending and under prosecution.

New Rejection

(necessitated by amendment)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 6-10, 14-17, 27, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites "**lacking at least** amino acids 495-517, 525-547, and 555-575 of the Zinc finger region of human Sp3". It is unclear if this phrase limits the lack of amino acids to the Zinc finger region or if it encompasses amino acids anywhere in the fusion protein. If Applicants intended to limit the lack of amino acids to the zinc finger region, Examiner suggests wording such as "wherein amino acids 495-517, 525-547, and 555-575 are lacking from the zinc finger region of human Sp3" to clarify.

New Rejection

(based on new considerations)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 6-10, 14-17, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of identifying an agent that activates TSA-responsive Sp3-mediated transcription, comprising: providing a cell having (a) a first vector comprising a first regulatory sequence operably linked to a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) a fragment of human Sp3 having (1) transcriptional activity, (2) comprising at least one glutamine rich region of a TSA responsive domain of human Sp3, and (3) lacking at least amino acids 495-517, 525-547, and 555-575 of the Zinc finger region of human Sp3, and (ii) a DNA binding domain of a heterologous protein; and (b) a second vector comprising a target binding sequence for the DNA binding domain of the fusion protein operably linked to a reporter gene; contacting the cell with a test agent; and selecting a test agent that increases the expression of the reporter gene compared to a control.

The specification discloses Sp3 is involved in the transcriptional activation of p/21/WAF1/Cip1 by Trichostatin A (TSA) (p. 4, lines 16-17; Example 4) and that TSA, a well known histone deacetylase (HDAC) inhibitor, has a tumor-suppressing effect (p. 3, lines 22-23). The specification discloses that sodium butyrate and TSA activated p/21/WAF1/Cip1 gene promoter through the Sp1 binding sequence (p. 2, lines 11-12). The specification discloses that it is thought that the treatment and prevention of cancer are possible by enhancing the activity of Sp3 that suppresses cell neoplasia (p. 5, lines 19-21). The specification discloses "the inventors thought it might be possible to screen

for an anticancer agent targeting a novel molecule by identifying a new molecule involved in the signal transduction leading to the activation of the p21/WAF1/Cip1 promoter in response to a TSA stimulus" (p. 3, lines 25-28) and "the method of this invention for screening an anticancer agent is based on the finding by the inventors that Sp3 is involved in the signal transduction leading to the expression of antitumor effects in response to a TSA stimulus" (p. 5. lines 22-24). The specification discloses that "the system developed by the inventors for detecting the transcriptional activity of Sp3 using a reporter gene can also be used for screening of a compound that has an antitumor effect similar to TSA" (p. 5, lines 24-27), "if this assay system using the reporter gene is employed, an efficient, Sp3-mediated screening of an anticancer agent is possible by detecting the reporter activity in the cell after contacting the test sample and the cell" (p. 6, lines 13-16), and "a compound of this invention which enhances the transcriptional activity mediated by Sp3 is thought to be applicable to a wide range of tumors" (p. 10, lines 16-17). It appears the only intended use of an agent identified by the claimed method is for an anti-proliferative or anticancer agent. The specification, however, does not provide a nexus between agents identified by the claimed two-hybrid system and their anti-proliferative and anticancer effects. Further, the specification does not provide a nexus between agents identified by the claimed two-hybrid system and their function in activating Sp3-mediated transcription in any cells either *in vivo* or *in vitro*.

The specification further discloses that a "cell" includes human cells, mammalian cell, and MG63 human osteosarcoma cells. A cell can also include a yeast or bacterial cell (p. 9, lines 10-15). The term "cell" as disclosed by the specification is not limited and

encompasses both *in vivo* cells in intact hosts, as well as any *in vitro* cells in culture derived from any source and of any etiology.

The claims are not enabled because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention for identifying an agent that activates TSA responsive Sp3-mediated transcription in cells either *in vivo* or *in vitro* and that would also function as an anticancer agent. It is clear that TSA has known anti-tumor effects and that it activates Sp3 under certain conditions (p. 7, lines 4-15; Example 3), however, it is not clear how the identification of any agent that activates Sp3 in the claimed two-hybrid system predictably identifies an agent having cellular anti-proliferation activity or anticancer activity. The specification does not provide a nexus between agents identified by the claimed two-hybrid system and their function in activating Sp3-mediated transcription in any type of cell *in vivo* or *in vitro*, or their anti-proliferative and anticancer effects. No correlation was demonstrated between an agent that activated Sp3 transcription in the two-hybrid system and reduced tumor growth and antiproliferative effects. Thus, the claims are not enabled for a method of identifying an agent that activates TSA-responsive Sp3-mediated transcription using the two-hybrid system as claimed.

The specification provides no guidance on or exemplification of how to use the instant method to screen for a reagent that will bind and activate transcription *in vivo*. Allen et al (TIBS, 1995, 20:511-516) teach that while the two-hybrid system is useful for studying protein-protein interactions via activation of reporter-gene expression, there are several limitations and problems, and its application is limited (p. 512, col. 2). Allen

et al specifically teach that the most critical consideration in performing two-hybrid screens is whether true positives isolated in the system are actually representative of *in vivo* cellular interactions. "It is possible to identify interacting partners that never associate in vivo because they are normally expressed in different cell types, localized in distinct cellular compartments, expressed at different developmental stages etc" (page 513, col. 1, last para). Further, Fields and Sternglanz (TIG, 1994, 10:287-292) specifically teach that interaction of the target and library-encoded proteins does not necessarily indicate that they normally interact *in vivo* since the two-hybrid system may assay an interaction between domains that are not accessible in the native protein (p. 291, col. 1, last paragraph). In view of the unpredictability in the art pertaining to the identification of true positive binding reagents and the lack of correlation to *in vivo* results as discussed above, one of skill in the art could not predictably identify an agent that activates TSA-responsive Sp3-mediated transcription *in vivo* or that would function as an anti-proliferative or anti-cancer agent as contemplated. Similarly, one of skill in the art could not predictably identify an agent that activates TSA-responsive Sp3-mediated transcription or has anti-proliferative activity for *in vitro* cell culture comprising any type of cell, because the two-hybrid system is not predictably representative of the normal protein distribution or protein interactions found in cells even in cell culture.

The art teaches the complexity involved with Sp3 activated transcription. Black et al (J of Cellular Physiology, 2001, 188:143-160) teach that 'Sp1 site'-dependent transcription is involved in many signal transduction pathways linked to cancer, and this role in signal transduction has been shown to directly impinge on transformation. For

example, Sp1 and Sp3 DNA-binding activity are increased in epithelial tumors compared with papillomas, indicating increased activity of these factors contributes to tumor progression in skin, however, as seen with regulation of transcription, the role of these proteins in cancer is context-dependent (p. 147, col. 2). Black et al teach overlapping DNA binding specificities but different transcriptional properties of related Sp proteins. Black et al teach that Sp3 has been found to activate or repress transcription, dependent on the cell line or promoter examined, meaning the transcriptional property of Sp3 is context-dependent (p. 145, col. 1). Black et al teach that studies indicate that, depending on the promoter, upregulation of 'Sp1 site'-dependent transcription can be related to positive or negative changes in cell growth (p. 144, col. 1). Overlapping DNA binding specificities at 'Sp1-sites' for Sp factors yet different transcriptional properties of Sp factors demonstrate the differential expression of positively and negatively acting Sp and related proteins. For example, an Sp3 protein with an intact DNA binding domain can compete with Sp1 for promoter binding and regulate transcription at 'Sp1 site'-containing promoters by inhibiting promoter activity in an Sp1-dependent manner. Competition for promoter binding is a viable means for regulating transcription at 'Sp1 site'-containing promoters (p. 145, col. 2). Black et al teach that repressive, shorter isoforms of Sp3 can also inhibit Sp1/Sp3-dependent transcription by DNA binding-independent mechanisms that appears to involve competition for components of the basal transcription machinery (p. 145, col. 2). The teachings of Black et al indicate that the role of Sp3 in cell growth or growth inhibition is context-dependent and that many factors play a role in the cellular pathways involving

'Sp1 site'-containing promoters. Considering the teachings of Black et al, it could not be predicted that an agent that increases Sp3 transcriptional activity would predictably identify that the agent has cellular anti-proliferative or anticancer activity or would predictably activate TSA-responsive Sp3- mediated transcription *in vivo* or *in vitro*. Considering the teachings of Black et al, there are many factors involved in the activation or repression of promoters containing 'Sp1 sites' such as p21/WAF1/Cip1 (as used in the two-hybrid system taught by the specification), and the activity of Sp3 is extremely context-dependent, hence, it could not be predicted that that an agent that activates TSA-responsive Sp3 mediated transcription using the claimed two-hybrid system could predictably identify an agent that activates TSA-responsive Sp3 mediated transcription either *in vivo* or *in vitro* cells or identify agents having cellular anti-proliferative or anticancer activity. A high quantity of experimentation would be necessary to practice the invention as claimed.

Finally, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Zips et al (2005, In Vivo, 19:1-7) teach "It is obvious that cells in culture represent

an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularization, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential (p. 3, col. 2)." One of skill in the art could not reasonably extrapolate the results of a system comprising a cell having a two-hybrid reporter system *in vitro* to the identification of an agent that would activate TSA-responsive Sp3-mediated transcription *in vivo* or predictably identify an agent having antiproliferative or anticancer effects.

Therefore, in view of complex nature of the invention, the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

4. All other rejections recited in the Office Action mailed April 9, 2007 are hereby withdrawn.

5. **Conclusion:** No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642